REMARKS

Prior to entry of the amendments presented above, claims 1-21 were pending in the application. Claims 5, 6, 19 and 20 have been canceled and claims 22 and 23 have been added.

In the January 4, 2007 Office Action, claim 1 was rejected for obviousness-type double patenting over claims 1 and 17 of copending application 10/766,312. Claims 1, 8, 11 and 12 were rejected under § 102(e) as anticipated by Stemmer. Claims 1-4, 7, 11, 15-18, and 21 were rejected under 35 U.S.C. 103(a) as being unpatentable over Blaschke in view of both Stemmer and Varadaraj, as evidenced by Swerdlow. Claims 1, 9, 11 and 13 were rejected as obvious over Stemmer in view of Kyle. Claims 1 and 8-14 were rejected as obvious over Stemmer and Kyle further in view of the Sigma catalog and Wierenga. The specific grounds of objection, and applicants' response thereto, are set forth in detail below.

Interview

Applicants thank the Examiner for the courtesy of the in-person interview conducted at the USPTO on November 17, 2006. The comments set forth below reflect the issues discussed during the interview. As also discussed at the interview, applicants file herewith an Information Disclosure Statement (IDS), and discuss below the content of the cited references.

Information Disclosure Statement

Applicants file herewith an Information Disclosure Statement (IDS), along with Form PTO-1449. The discussion below addresses US patents 5,985,569 to Foxall *et al.* and 5,962,273 to Durmowicz *et al.*

Rejection Under 35 U.S.C. §102

Stemmer

The Examiner has maintained the prior rejection of claims 1, 8, 11 and 12 under § 102(e) as anticipated by Stemmer. Specifically, the Examiner reiterates the assertions set forth in the Office Action of April 12, 2006 that Stemmer teaches that antifoam reagents can be used in PCR reactions. Moreover, the Examiner asserts that one of skill in the art would have recognized the utility of antifoam reagents in PCR because the art allegedly teaches that proteins, such as polymerases, are inactivated by foaming. Applicants previously noted that Stemmer fails to

describe either the identity or the concentration of any suitable antifoam reagents for use in PCR and, in response, the Examiner states that the instant claims do not specify either the nature or the identity of the antifoam. Applicants respectfully traverse the rejection.

As an initial matter, applicants note that there is no art of record in this case that states that polymerases are inactivated by foaming –indeed, applicants are not aware of evidence that this is the case. Accordingly, applicants respectfully submit that the Examiner's statements regarding the motivation to add antifoam to a PCR reaction to prevent protein inactivation are inapposite.

Applicants previously have described why Stemmer is not an enabling reference, since there is no teaching in Stemmer that would have taught one of skill in the art how to make ad use an antifoam reagent in a PCR reaction. In particular, Stemmer neither identifies any antifoam reagent that would have worked in a PCR, nor describes an appropriate concentration of that antifoam.

In further support of this contention, applicants submit herewith a Declaration under 37 CFR § 1.132 by Mr. Mark Berninger ("the Berninger Declaration") a researcher skilled in the molecular biological arts. Mr. Berninger's declaration addresses the rejection as set forth in the April 12. 2006 office action; however, that rejection is identical in substance to the rejection set forth in the instant office action and therefore Mr. Berninger's comments are equally relevant to the instant action. Mr. Berninger states that the alleged teachings of Stemmer are deficient in several respects. For example, Stemmer's guidance as to PCR reaction conditions (*i.e.*, the description provided at column 30, lines 7 to 30 of Stemmer) is not instructive so as to enable one of ordinary skill in the art to practice PCR as it is generally performed in the field, and in fact, would lead one away from performing PCR according to established and accepted protocols. See, Berninger Declaration at ¶ 7. Mr. Berninger also indicates that the nondescript recitation of "anti-foam" is antithetical to proper PCR protocols. *Id.* Mr. Berninger states that PCR requires tightly controlled reaction conditions, and is a repetitive process whereby any small variation in reaction efficiency is magnified due to the exponential increase in product formed as the PCR proceeds over dozens of cycles. See, Berninger Declaration at ¶ 8. Mr. Berninger asserts that he would never use the general direction as to anti-foam agents offered in Stemmer, and that he would not allow those under his direction to use such a protocol. *Id.*

For these reasons, Mr. Berninger concludes that Stemmer's teachings of the use of anti-foam are deficient. Thus, since Stemmer would not have enabled one skilled in the art to have selected and used an appropriate antifoam reagent without undue experimentation, Stemmer is not an enabling reference. Applicants assert that this rejection is improper and should be withdrawn.

The Examiner asserts that Stemmer's failure to identify a suitable antifoam nor provide suitable concentrations are not relevant because the instant claims do not specify particular antifoams or concentrations. However, one does not look to the claims but to the specification to find out how to practice the claimed invention. MPEP 2164.08 (citing *W.L. Gore & Assoc., Inc. v. Garlock, Inc.*, 721 F.2d 1540, 1558, 220 USPQ 303, 316-17 (Fed. Cir. 1983); *In re Johnson*, 558 F.2d 1008, 1017, 194 USPQ 187, 195 (CCPA 1977). Accordingly, it is not necessary for the claims to specify either the nature of the antifoam, nor concentrations. The instant specification fully describes antifoam reagents that are suitable for carrying out PCR reactions and also details suitable concentrations. By contrast, Stemmer provides neither and, for the reasons set forth above and as described by Mr. Berninger, would not have enabled one skilled in the art to practice the claimed invention. Accordingly, applicants respectfully submit that this rejection is improper and should be withdrawn.

Rejections Under 35 U.S.C. §103(a)

Blaschke in view of both Stemmer and Varadaraj, as evidenced by Swerdlow

Claims 1-4, 7, 11, 15-18, and 21 are rejected as obvious over Blaschke in view of both Stemmer and Varadaraj, as evidenced by Swerdlow. Applicants respectfully traverse.

Specifically, the Examiner asserts that Blaschke teaches real-time RT-PCR methods but does not teach use of detergents or anti-foam reagents. Stemmer is cited as providing the motivation to add detergents and antifoam reagents Varadaraj is cited as teaching that detergents improve the specificity of the amplification process. Swerdlow is cited as teaching that air bubbles interfere with microfluidic technology and that detergents create air bubbles. Based upon this combination of no less than four references, the Examiner concludes that the claimed invention would have been *prima facie* obvious. Applicants respectfully traverse because the Examiner has failed to describe why one of ordinary skill in the art would have been motivated

to combine the cited references, and has failed to provide appropriate evidence that there was a reasonable expectation of success in making the combination. Accordingly, no p*rima facie* case of obviousness exists and the rejection should be withdrawn.

First, although Varadaraj may suggest that in certain circumstances certain detergents may be added to a PCR, it also states that ethanol *inhibited* PCR amplification. The www.dermaxime.com/alcohol.htm website cited by the Examiner states that ethyl alcohol (ethanol) is an antifoam. This result confirms the findings in the present application, namely that certain antifoams are deleterious in PCR reactions. Accordingly, Varadaraj teaches that addition of an antifoam is deleterious to PCR and therefore teaches directly away from the instantly claimed invention. Indeed, Varadaraj confirms the surprising nature of the results obtained by the applicants that certain antifoams at particular concentrations can be used in PCR reactions without substantially inhibiting the reaction.

In response to applicants' prior arguments on this point, the Examiner asserts that Vadaraj does not "teach that all antifoam agents inhibit PCR." Applicants respectfully submit that, whether or not this is true, it is not relevant to the instant rejection. Vadaraj discloses a single compound that, under the Examiner's previously stated rationale, is an antifoam, and describes unequivocally that this compound inhibits PCR. This is all that a "teaching away" requires. It is improper to combine references where the references teach away from their combination. MPEP 2145. Vadaraj teaches away from using an antifoam in a PCR and therefore cannot properly be combined with other references in support of the instant rejection.

Second, it is not at all clear what causes the bubbles in the method described by Swerdlow. Nothing in Swerdlow mentions that a detergent was used in the described method, so the source of the bubbles is a mystery. The bubbles could well have been generated after the PCR reaction during the liquid flow from the PCR reaction to the chromatography column and in that case there would have been no motivation whatsoever to add an antifoam to the PCR reagent. Moreover, if it was so obvious to use an antifoam to prevent bubbles, why did Swerdlow not simply add an antifoam? Swerdlow's failure to teach or suggest use of an antifoam speaks volumes regarding the Examiner's arguments regarding obviousness. In any event, nothing in any of the cited references teaches or suggests that an antifoam reagent would be useful to remove the type of bubbles described by Swerdlow.

Third, Blaschke describes PCR methods and specifically describes obtaining single band PCR products (see page 83, right hand column) so one of ordinary skill in the art would have had no motivation to modify the teachings of Blaschke in the manner posited by the Examiner, let alone have the motivation to add detergent to the PCR mixture. Fourth, Stemmer is not an enabling reference for the reasons described above and as set forth in the declaration by Mr. Berninger, and would not have taught or suggested the instantly claimed invention to one of ordinary skill in the art. Moreover, the actual results described by Varadaraj that the antifoam ethanol *inhibited* PCR clearly would have led one of ordinary skill in the art to conclude that Stemmer's vague recitations regarding additives that might or might not be useful in PCR were unreliable and non-enabling.

In sum, Varadaraj clearly teaches away from the instant invention, and there would have been no motivation to combine Blaschke with any of the secondary references since Blaschke reports obtaining good results from PCR reactions in the absence of any foam-causing detergent or other source of foam. There is nothing in Swerdlow to indicate that there would have been any reason to add an antifoam to a PCR reaction, nor does Swerdlow teach or suggest that an antifoam would be a useful way of removing bubbles. Stemmer is non-enabling for all the reasons described above. Accordingly, nothing in the combination of references cited by the Examiner would have motivated one of ordinary skill in the art to use an antifoam reagent in a PCR reaction and no *prima facie* case of obviousness exists, and the rejection should be withdrawn.

Stemmer in view of Kyle

Claims 1, 9, 11 and 13 are rejected as obvious over Stemmer in view of Kyle. Specifically, the Examiner asserts that Stemmer suggests using detergent and antifoam in a PCR but fails to teach or suggest use of 1520-US as the antifoam. Kyle is cited as teaching that 1520-US is an antifoam. Applicants respectfully traverse.

The deficiencies of Stemmer are described above, and in detail in the Berninger Declaration. Kyle fails to cure these deficiencies, since, like Stemmer, there is nothing in Kyle that would have provided one of ordinary skill in the art with a reasonable expectation of success in using *any* antifoam, let alone 1520-US in a PCR reaction. Accordingly, no *prima facie* case of obviousness exists and Applicants respectfully request withdrawal of the rejection.

Stemmer and Kyle further in view of the Sigma catalog and Wierenga

Claims 1, 8, 10-12 and 14 were rejected as obvious over Stemmer and Kyle further in view of the Sigma catalog and Wierenga. Specifically, Stemmer and Kyle are cited for the same propositions as above, but do not describe using combinations of antifoams. The Sigma catalog is cited as suggesting that antifoams can be used in combination and Wierenga is cited as teaching that a combination of the silicone and organic antifoams are synergistic. The Examiner asserts that it would have been obvious to combine the cited references to arrive at the instantly claimed invention. Applicants respectfully traverse.

The deficiencies of Stemmer and Kyle are set forth above and are not cured by either the Sigma catalog or Wierenga. Neither the Sigma catalog nor Wierenga teach or suggest that antifoams might be useful in a PCR reaction. In addition, nothing in the Sigma catalog teaches or suggests that combinations of antifoams would be useful *in a PCR reaction.* Thus, no *prima facie* case of obviousness exists and the rejection should be withdrawn.

References submitted herewith

Foxall et al.

US patent 5,985,569 to Foxall *et al.* ("Foxall") is cited in the IDS filed herewith. Foxall discloses a method for detecting a bacterium using a nucleic acid amplification method known as strand displacement reaction (SDA). SDA is quite different from PCR and the reaction conditions for the two amplification processes are distinct. Accordingly, the disclosure contained in Foxall is not relevant to PCR reactions.

This distinction is further described by Mr. Berninger. See, Berninger Declaration at ¶¶ 9-10. Mr. Berninger notes that Foxhall mentions the use of an anti-foam in three of the examples, which include optimization of SDA conditions. *Id.* Tellingly, Mr. Berninger notes that in the description of the conditions identified as producing the greatest amplification using SDA, anti-foam is not included. Mr. Berninger thus concludes that one skilled in the art would not be led to use anti-foam in SDA since the use of this agent is not adequately described.

Durmowicz et al.

US patent 5,962,273 to Durmowicz *et al.* ("Durmowicz") is also cited in the IDS filed herewith. Durmowicz describes use of SDA to detect *Neisseria gonorrhoeae*,. As described above, SDA and PCR are quite different processes and the reaction conditions for SDA are very different from those of PCR.

Mr. Berninger indicates that Durmowicz discloses the use of an anti-foam agent; 0.015% antifoam is provided as the last compound in a listing of reaction components in Example 14, but that the type of antifoam to be used is not disclosed. See, Berninger Declaration at ¶ 11. Mr. Berninger notes that it is recognized in the field that many types and qualities of antifoam are available commercially, so that a general instruction to use 0.015% antifoam is not sufficiently descriptive for even a practitioner with substantial experience in the field of nucleic acid amplification. *Id.* Mr. Berninger distinguishes anti-foam agents from defined compounds such as glycerol or DMSO, both of which are also included in specific amounts (8% and 3%, respectively) in the reaction conditions listed in Example 14. *Id.* Mr. Berninger contrasts these defined compounds with anti-foam agents, which could be a single compound or a mixture of compounds, requiring a skilled practitioner to laboriously test essentially all anti-foams and combinations thereof at a range of concentrations around 0.015% in an attempt to find the anti-foam agent(s) which work optimally at a concentration of 0.015%. *Id.*

Mr. Berninger thus concludes that one skilled in the art would not be led to use anti-foam in SDA since the use of this agent is not adequately described. *Id.*

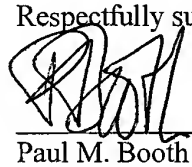
CONCLUSION

In view of the foregoing remarks, Applicants respectfully submit that the claims are in condition for allowance and request a prompt notification to this effect.

Should the Examiner feel that there are any issues outstanding after consideration of this response, the Examiner is invited to contact the undersigned to expedite prosecution of the application.

The Commissioner is hereby authorized by this paper to charge any fees during the entire pendency of this application including fees due under 37 C.F.R. §§ 1.16 and 1.17 which may be required, including any required extension of time fees, or credit any overpayment to Deposit Account 50-3840. **This paragraph is intended to be a CONSTRUCTIVE PETITION FOR EXTENSION OF TIME in accordance with 37 C.F.R. § 1.136(a)(3).**

Respectfully submitted,



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